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Letter

Convergent Synthesis of Calcium-Dependent Antibiotic CDA3a and Analogues with Improved Antibacterial Activity via Late-Stage Serine Ligation

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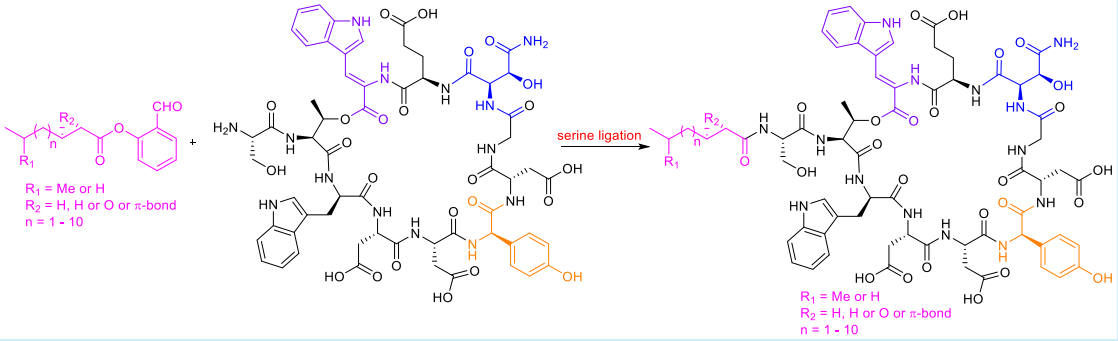
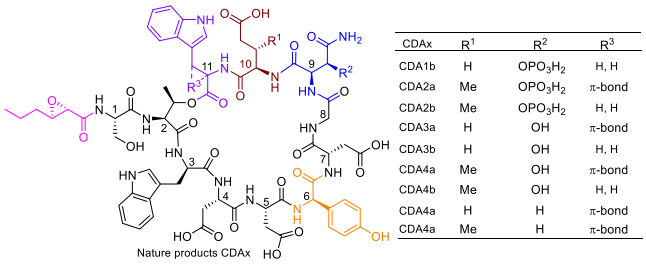


ABSTRACT: A convergent synthesis via the late-stage serine ligation of naturally occurring calcium-dependent antibiotic CDA3a and its analogues has been developed, which allowed us to readily synthesize the analogues with the variation on the lipid tail. Some analogues were found to show 100−500-fold higher antimicrobial activity than the natural compound CDA3a against drug resistant bacteria. This study will enhance our understanding of CDA3a and provide valuable antibacterial lead candidates for further development.

The rapid emergence of widespread bacterial resistance to existing antibacterial drugs has become an urgent global threat to human health, which calls for the development of new antibiotics.[1] Cyclic peptides have been an important class of modalities as antibacterial agents,[2] such as vancomycin, bacitracin, colistin/polymyxin, gramicidin, and daptomycin, all being clinically used. New cyclic peptides with promising antibacterial profiles have been discovered in recent years, including teixobactin,[3] malacidins,[4] cadaside,[5] and darobactin,[6] which hold promise for future clinical applications. Among all these antibacterial cyclic peptides, daptomycin,[7,8] A54145,[9,10] malacidins,[11] and cadaside[12] are grouped into calcium dependent antibiotics, which require the Ca^{2+} in serum to exert their antibacterial acts. They contain a distinct calcium binding motif (Asp-Xaa-Asp-Gly) responsible for calcium binding.[13,14]

The calcium-dependent antibiotics (CDAs)[15−17] were first extracted from *Streptomyces coelicolor* A3(2) (Figure 1). It comprises an exocyclic tail containing a serine and N-terminal fatty acid side chain (a *trans*-2,3-epoxyhexanoyl moiety), along with a cyclic decadepsipeptide. Based on the complete genome sequence of CDAs' producer *Streptomyces coelicolor* A3, the biosynthesis of CDAs has been established and later engineered to produce CDAs' analogues.[18−27] Due to bioengineering restrictions, the modifications were limited to the specific amino acid residues, and none of the generated analogues showed comparable or improved antibacterial activity compared to the natural compound. Chemical synthesis would promise to overcome the bioengineering limitation in generating analogues; however, the total synthesis of CDAs has not been reported yet.



CDAx	R^1	R^2	R^3
CDA1b	H	OPO_3H_2	H, H
CDA2a	Me	OPO_3H_2	π-bond
CDA2b	Me	OPO_3H_2	H, H
CDA3a	H	OH	π-bond
CDA3b	H	OH	H, H
CDA4a	Me	OH	π-bond
CDA4b	Me	OH	H, H
CDA4a	H	H	π-bond
CDA4a	Me	H	π-bond

Figure 1. Structures of CDA3a and its congeners.

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CDA3a features an unusual *trans*-2,3-epoxyhexanoyl exocyclic tail, together with three nonproteinogenic amino acid residues including *Z*-dehydrotryptophan at position 11, D-4-hydroxyphenylglycine (D-Hpg) at position 6, and (2*R*,3*S*)-3-hydroxyasparagine (3-HOAsn) at position 9.[15−17] The notable structural motif is the *Z*-dehydrotryptophan residue. The planar geometry at α,β-carbons of *Z*-dehydrotryptophan profoundly reduces the conformational flexibility of CDA3a, which can also confer resistance to enzymatic degradation and alter bioactivity.[28,29] Dehydrotryptophan is found in many natural products.[29] The syntheses of several dehydrotryptophan amino acid and dipeptide derivatives have been reported;[29] however, the total synthesis of dehydrotryptophan-containing large peptides is yet to be developed. Prompted by its unique structural features, antibacterial activity, and availability of the high-quantity NMR spectrum, we set out to develop the total synthesis of CDA3a, which further enables us to carry out the structure−activity relationship studies to develop analogues with improved antibacterial profiles.

Our retrosynthetic route of CDA3a was devised as a convergent synthesis of linking the cyclic peptide core and the acyl chain via a chemoselective Ser ligation[30−32] (Figure 2),

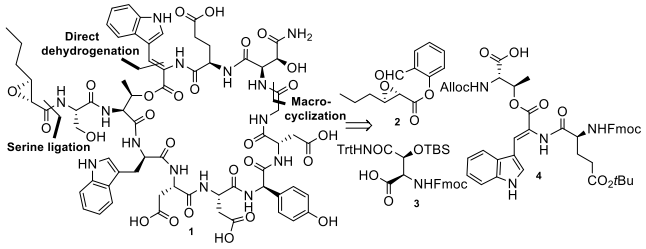
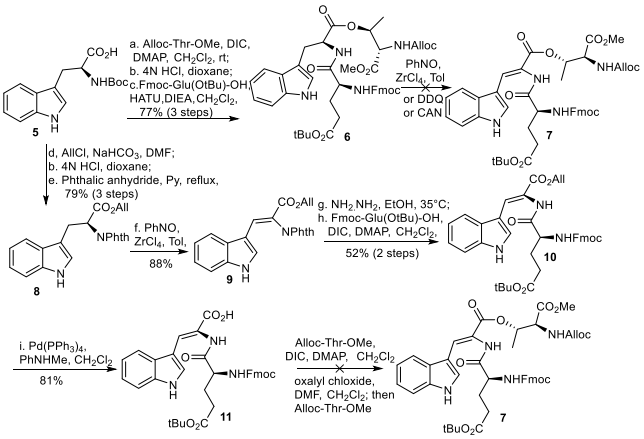


Figure 2. Retrosynthetic analysis of CDA3a.

which would generate CDA3a and further derivatives with variation of the fatty acyl substituent from a common precursor. The acid labile *trans*-2,3-epoxyhexanoyl tail cannot tolerate the last step global deprotection condition (95% TFA/5% H_2O) with the conventional strategy using the side-chain protected peptide precursor, thus another rationality for our Ser ligation-based synthetic route is to avoid using strong acidic conditions with the *trans*-2,3-epoxyhexanoyl group being present. The macrocyclization site is selected between 3-HOAsn and achiral amino acid glycine to avoid the epimerization issue during the cyclization. Another foreseen challenge lies in the esterification between *Z*-dehydrotryptophan and threonine, as the reactivity of *Z*-dehydrotyptophan is not fully documented in the literature.

The synthesis of the requisite 3-HOAsn **3** has been reported in our previous synthesis of A54145.[33] Foreseeing the challenge of on-resin esterification between *Z*-dehydrotryptophan and threonine, we planned to construct a *Z*-dehydrotyptophan-containing tripeptide building block **4** via solution phase reactions, which is suitable for Fmoc-SPPS (solid phase peptide synthesis). As shown in Scheme 1, a direct dehydrogenation precursor **6** was first prepared through coupling, deprotection, and coupling with the commercially available compound **5**. Then the direct dehydrogenation[34,35] of the tripeptide **6** was screened with a variety of oxidants such as DDQ, CAN, and PhNO/$ZrCl_4$; none of which were successful. Therefore, we modified the synthetic sequence and conducted the direct dehydrogenation on the Trp residue first. According

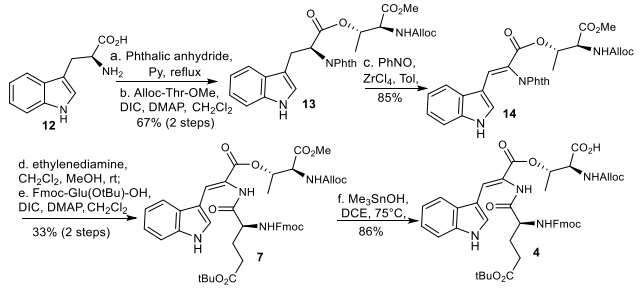
Scheme 1. Unsuccessful Routes Towards Tripeptide 4



to the new strategy, the carboxylic acid of **5** was first protected with allyl, followed by Boc deprotection and amine reprotection with phthalimide. The obtained **9** was subjected to the direct dehydrogenation to provide the corresponding product **10** in 88% yield as a single *Z*-isomer which is thermodynamically more stable than the *E*-isomer.[29] Then, removal of the *N*-Phth group and treatment with freshly prepared glutamic acid anhydride were followed by deprotection of the allyl group to afford the carboxylic acid. Unfortunately, esterification of **11** failed under a variety of attempted conditions. Apparently, the unsaturation dramatically deactivates the reactivity of the carboxylic acid.

To overcome the above obstacle, we adjusted the sequence of formation of esterification and amidation. As shown in Scheme 2, the protection of the primary amino group of **12**

Scheme 2. Synthesis of Tripeptide 4



with phthalic acid was followed by coupling with Alloc-L-Thr-OMe to give **13** in a moderate yield. Then a direct dehydrogenation of **13** was conducted to provide the corresponding depsidipeptide **14** in 85% yield as a single *Z*-isomer. Sequential treatment of **14** with ethylenediamine to release the free amine followed by amidation by being treated with freshly prepared symmetric anhydride of Fmoc-Glu-(OtBu)-OH afforded **7** in 33% yield over 2 steps. Selective hydrolysis of the methyl ester of **7** could be achieved by being treated with Me_3SnOH[36] to give the desired tripeptide **4** in 86% yield. Collectively, our results showed that dehydrotryptophan has the deactivated carboxylic acid group but maintains the amino reactivity toward acylation.

Next, the synthesis of epoxyhexanoyl salicylic aldehyde ester was based on the Sharpless asymmetric epoxidation.[37] As depicted in Scheme 3, asymmetric epoxidation of the known allylic alcohol **15** provided epoxide **16**. Treatment of 2*S*,3*S*-**16**

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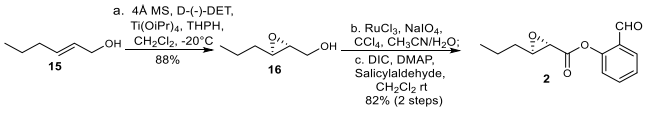
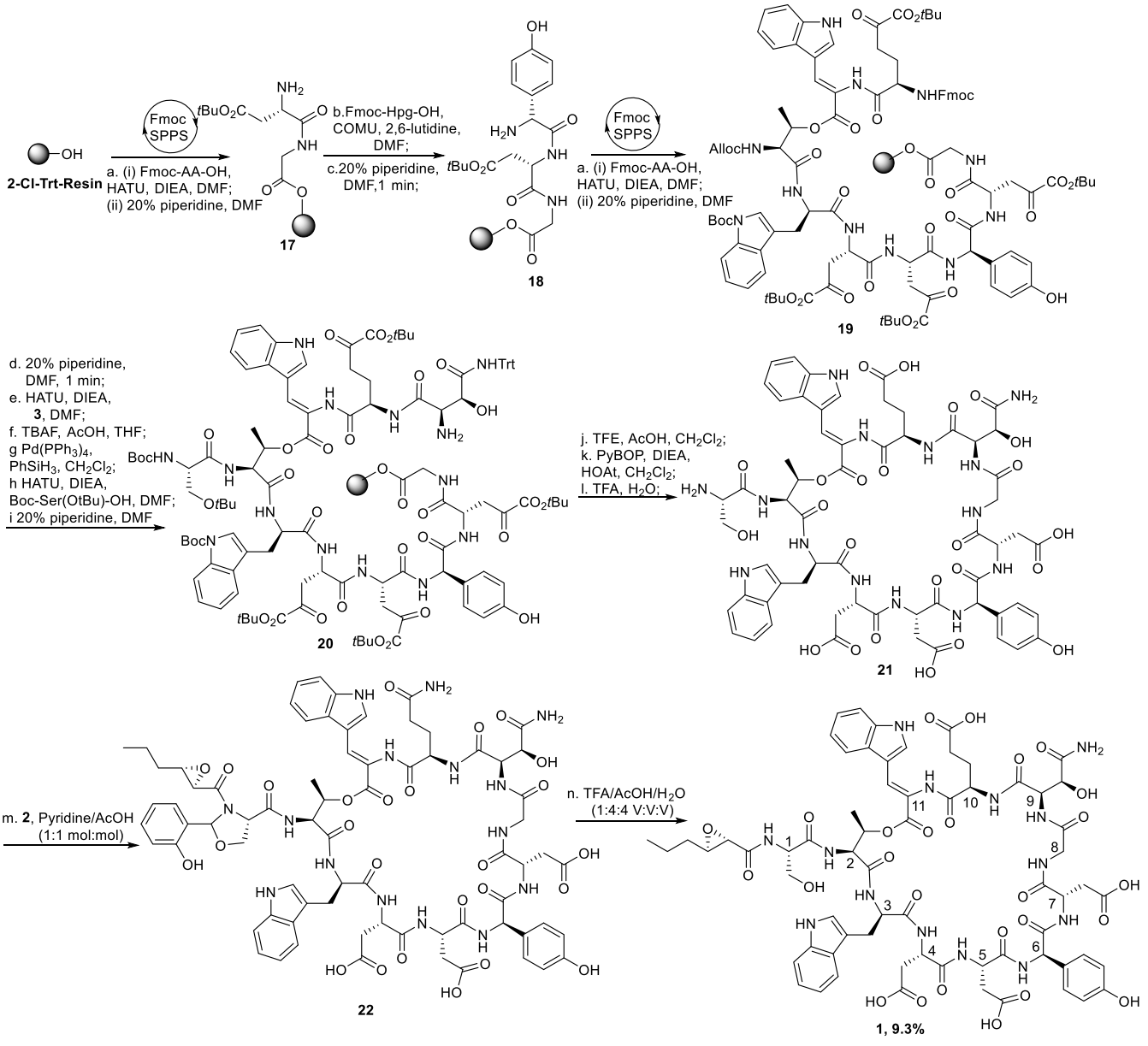
Scheme 3. Synthesis of Epoxyhexanoyl Salicylic Aldehyde Ester 2



with ruthenium chloride and sodium periodate produced carboxylic acid in nearly quantitative yield. The optically active key carboxylic acid was coupled with salicylaldehyde in the presence of DIC to afford the epoxyhexanoyl salicylaldehyde ester **2** in 82% yield over two steps.

With all building blocks in hand, we continued with the total synthesis of CDA3a. According to the retrosynthesis analysis, the Fmoc-Gly-OH was incorporated into a 2-chlorotrityl chloride resin to start Fmoc-SPPS. Due to the high proneness to epimerization of the D-Hpg during SPPS,[38−40] different conditions for Fmoc-removal and different coupling reagents were tested (see Table S1). COMU in combination with 2,6-lutidine proved to the best condition for coupling D-Hpg as shown in Scheme 4. Then the resultant resin-linked peptide was subsequently coupled with Fmoc-L-Asp-OH, Fmoc-D-Trp-OH, and *Z*-dehydrotyptophan-containing tripeptide **4** to afford **19**. In order to avoid facile 2,5-diketopiperazine formation, the deprotection of the Fmoc group used 20% piperidine in DMF for 1 min to release free amine, which immediately underwent amidation with 3-HOAsn **3**. Then deprotection of TBS and the Alloc group released the free amino group. It was noted that in order to avoid an intramolecular *O*-to-*N* acyl shift, the time of the deAlloc step could not be more than 1 h. The resulting free amino group was coupled with Boc-L-Ser(O*t*Bu)-OH under standard conditions to afford the desired linear peptide chain **20**. After deprotecting the N-terminal Fmoc group of the linear peptide, the side chain protected linear peptide was released from the trityl resin with AcOH/TFE/CH_2Cl_2 to give rise to the acyclic precursor. The macrocyclization proceeded

Scheme 4. Synthesis of Syntheses of CDA3a



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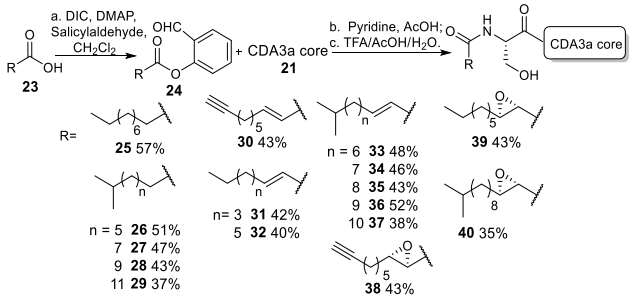
smoothly in CH_2Cl_2 with PyBOP/HOAt/DIEA as the coupling reagent to afford the cyclic peptide. Then the global deprotection of the side chain protective group gave rise to the desired cyclic core **21**. It is worth noting that if the cocktail was changed to TFA/TIPS/H_2O (95/2.5/2.5, v/v/v), the double bond in *Z*-dehydrotryptophan was reduced.

With the cyclic core **21** in hand, serine ligation was then used to complete the total synthesis of CDA3a as shown in Scheme 4. The ligation proceeded efficiently to couple **21** and **2** in pyridine/AcOH (1:1, mol:mol) with a complete conversion to afford the intermediate **22** in 6 h, and then the *N,O*-benzylidene acetal intermediate was treated with TFA/AcOH/H_2O (1:4:4, v/v/v) for 3 h to give the desired CDA3a **1** in 9.3% yield based on the 100 mg resin (0.05 mmol loading), after reversed-phase HPLC purification. It is worth mentioning that the acid hydrolysis of the *N,O*-benzylidene acetal intermediate with a low percent of TFA was accomplished cleanly without any epoxy ring opening product detected. The ^{1}H NMR data for synthetic CDA3a agreed with the reported one[19] for the natural product (see Figure S129). As a comparison, the epoxyhexanoyl pentafluorophenol ester failed to couple with CDA3a core **21** (Figure S2), which demonstrated the effectiveness and uniqueness of late-stage serine ligation for CDA3a synthesis.

To explore the significance of the acyl tail on its antibacterial activity, we also designed and synthesized a library of CDA3a analogues containing different lengths, different α,β-substitutions, or different terminal substitutions of acyl tails[41] (see the SI for synthetic details). Saturated acyl acids with different lengths (C_{10}, C_{12}, C_{14}, C_{16}) were coupled with salicylic aldehyde, followed by a subsequent serine ligation with cyclic core **21** giving **25**–**29** in 37%–57% yield (Scheme 5). The

Scheme 5. Synthesis of CDA3a Derivatives with Different Acyl Acid Tails



α,β-unsaturated analogues **30**–**37** with different lengths (C_8, C_{10}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}) or terminal-alkyne were prepared under identical conditions in 38%–52% yield. The α,β-epoxy analogues **38**–**40** with different lengths (C_{10}, C_{14}) or terminal-alkyne were also prepared expecting to be compared with the α,β-unsaturated analogues. After purification by reversed-phase HPLC, the α,β-epoxy analogues were isolated in 35%–43% yield over 2 steps

The synthetic CDA3a and all above-mentioned analogues were subjected to the assessment of their antibacterial activities by determining their minimal inhibitory concentration (MIC) on various Gram-positive bacteria strains including methicillin-susceptible *S. aureus* strain ATCC29213 and methicillin-resistant *S. aureus* clinical isolates. As shown in Table 1, synthetic CDA3a displayed poor anti-SA and anti-MRSA activity, similarly as reported.[9] Synthetic analogues **25**–**29**,

Table 1. Minimal Inhibitory Concentrations (in μg/mL) of CDA3a and Its Analogues

bacterial strain	MRSA SA1114	SA ATCC29213	*Streptococcus faecalis* SF	Enterococcus ATCCET
1	512	256	256	>1024[a]
25–**31**	>32[b]	>32[b]	>32[b]	>32[b]
32	8	4	>32[b]	>32[b]
33	8	4	4	4
34	4	2	>32[b]	>32[b]
35	4	4	8	8
36	4	4	16	16
37	8	8	4	4
38	>32[b]	>32[b]	>32[b]	>32[b]
39	8	2	>32[b]	>32[b]
40	2	2	2	2

[a]The highest concentration tested was 1024 μg/mL. [b]The highest concentration tested was 32 μg/mL.

whose side chain lengths were more than 10 carbons and saturated lipid acids, did not show any antibacterial properties as **31**, whose side chain lengths were less than 10 carbons and had an α,β-double bond, while the synthetic analogues **32**–**37**, **39**, and **40**, whose side chain lengths were equal to or more than 10 carbons and had an α,β-double bond or α,β-epoxy group, showed much improved antibacterial activity. Surprisingly, although the synthetic analogues **33**, **35**, **37**, and **40** containing an even number of carbons showed comparable antibacterial activity to *Streptococcus faecalis* SF and *Enterococcus* ET6, synthetic analogues **34** and **36** containing an odd number of carbons did not show any antibacterial activity to them. Unexpectedly, synthetic analogues **30** and **38**, which contain a terminal alkyne in the side chain, lost all the antibiotic activity. Therefore, the MIC result indicated that the side chain, including length, substituent at the α,β-position, and the terminal position, seemed to be important for potent antibacterial activity.

In summary, we have developed a convergent synthetic route for the total synthesis of the CDA3a via late-stage serine ligation, which was also used to prepare a small library of CDA3a analogues to establish a preliminary structure–activity relationship (SAR). The key features of the synthesis include a solution for the preparation of dehydrotryptophan-containing depsipeptides and a late-stage serine ligation. Several analogues with greatly enhanced antibacterial activity were identified, in particular with compound **40** being the most potent analogue with 256–512-fold greater potency against VRE and MRSA than the parent CDA3a. Our SAR studies showed that the length, α,β-substitution, and terminal substitution of a fatty acid tail are important for its bioactivity. We anticipate that the findings in this study will generate a new understanding of calcium dependent cyclic peptide antibiotics and provide a roadmap for further development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01544.

Experimental procedures, characterization data of synthetic compounds, and 1D and 2D NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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